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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,585	07/28/2006	Sumihiro Nomura	0283-0221PUS1	7194

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EXAMINER	
MCINTOSH III, TRAVISS C	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
06/30/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/566,585	NOMURA ET AL.	
	Examiner	Art Unit	
	TRAVISS C. MCINTOSH III	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *19* is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/15/06 & 1/31/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Objections

Claims 1 and 12 are objected to because of the following informalities: there appears to be a few misspellings, for example in the 7th line below the structure in claim 1 there should be a space between "are" and "there" (it is written "arethere"). Likewise, in the 4th to last line of claim 12, there should be a space in "arecombined" to make it "are combined". Appropriate correction is required. It is noted that this is not necessarily an inclusive list of all possible spelling mistakes.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 and 16-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 includes the limitation of various optionally "**substituted" rings**. In the absence of the identity of moieties which are intended to be substituted, thus modifying an art recognized

chemical core, described structurally or by chemical name, the identity of "substituted" would be difficult to ascertain. In the absence of said moieties, the claims containing the term "substituted" are not described sufficiently to distinctly point out that which applicant intends as the invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating diabetes with the compound of claim 1, does not reasonably provide enablement for treatment with the claimed combinations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)***. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:
(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

Claim 17 is drawn to a pharmaceutical composition comprising the compound of formula I and another antidiabetic agent. Claim 19 is drawn to combination therapy for treating diabetes.

The state of the prior art

Combination therapy, and drug-drug interactions are known in the art to have various effects, and when physicians use several drugs in combination, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction, and if so, how to take advantage of the interaction if it leads to improvement in therapy or how to avoid the consequences on an interaction if they are adverse. A potential drug interaction refers to the possibility that one drug may alter the intensity of the pharmacological effects of another drug if given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs, or the appearance of new effects which is not seen with either drug alone. The frequency of significant beneficial or adverse effects is unknown. The interaction between the drugs may be pharmacokinetic, i.e. alteration of the absorption, distribution, or elimination of one drug by another, or may be pharmadynamic, i.e. interactions between agonists and antagonists at drug receptors. The most important drug-drug interactions occur with drugs that have serious toxicity and low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences. Additionally, drug-drug interactions can be clinically important if the disease being controlled with the drug is serious or potentially fatal if left under

treated. Drugs are known to interact at any point during their absorption, distribution, metabolism, or excretion; the result being an increase or decrease in concentration of the drug at the site of action. As individuals vary in their rates of disposition of an given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable, but can be very significant. See Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Medical Publishing Division, 2001, pages 54-56.

The level of predictability in the art

As seen by Goodman & Gilman, the art of combination therapy is unpredictable. Drug-drug interactions are known to be beneficial or adverse, yet there is no way to known until the drugs are actually tested in an individual.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the claims as written. Applicants have not provided any indication of what drugs might be toxic and what the drugs therapeutic indexes are.

The existence of working examples

The working examples set forth in the instant specification are drawn to various methods of preparing the claimed compounds. There have been no experiments on humans or any animal models which would provide therapeutic use of any claimed compounds, nor combinations thereof.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable one to make or use the combination of the compound of claim 1 and any of the thousands of possible additional agents without undue experimentation. It is noted that the specification should teach how to make and use the invention, not teach how to figure out for oneself how to make and use the invention. See ***In re Gardner, 166 USPQ 138 (CCPA 1970).*** In order to practice the instant invention, one of ordinary skill in the art would be confronted with the undue burden to first determine if a drug actually performed any of the functionally described activities (i.e., test a compound to see if it is antidiabetic compound, or insulin analogue, or insulin secretion modulator, etc.). If the skilled artisan did determine if the drug had the activity, then they would be required to determine whether the drug would interact with the compound of formula III, first *in vitro*, and then *in vivo*. And if the drug did interact, the artisan would be required to determine how they interacted, did the interaction provide adverse effects or beneficial effects, or produce completely new effects? They would be required to determine at what point in the patients system the effect occurred, and determine what is needed to ensure the patient was effectively treated.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the salts of the claimed compounds, does not reasonably provide enablement for prodrugs of the claimed compounds. The claim(s) contains subject matter, which

was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention.

The breadth of the claims - The nature of the invention

The claims are drawn to various compounds, or salts or prodrugs of the same. The breadth of the claims includes all of the hundreds of thousands of compounds of formula I as well as the presently unknown list potential prodrug derivatives embraced by claim. The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body.

The state of the prior art

Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation. Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. (Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977.) The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate

the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) (Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, page 596) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to make or use the claimed compounds commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the claims as written. The examiner notes, there has not been provided sufficient instruction or sufficient methodological procedures to support the compounds instantly claimed.

The existence of working examples

There are no working example of a prodrug of any compounds.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be

an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Thus, undue experimentation will be required to determine if any particular compound of claim 1 is, in fact, a prodrug. Since the structures of these "prodrugs" are uncertain, direction for their preparation must also be unclear. Directions to a team of synthetic pharmaceutical chemists and metabolism experts of how to search for a "prodrug" hardly constitute instructions to the BS process chemist of how to make such a compound.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 8, 11, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al. (Ref CB from IDS filed 1/31/2006).

Lin et al disclose compounds anticipating those instantly claimed. See compounds 4a, c, d and e for example. It is noted that the acetyl groups on the sugar are known to be protecting groups used in chemistry.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Manis et al. (Ref. CA of Ids filed 1/31/2006).

Manis discloses compounds anticipating claims 1-5. See abstract disclosing MBOCA-glycoside. MBOCA is shown on page 169 and was thought to be an N-glycoside. Since the

Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Allowable Subject Matter

Claim 19 is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TRAVISS C. MCINTOSH III whose telephone number is (571)272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Traviss C McIntosh III/
Examiner, Art Unit 1623
June 21, 2008